REMARKS

I. Status of the claims

Claims 1, 14-16, 26, and 29-53 stand rejected. Claims 1, 32, 35, 36, 41, 46, 48, and 52 have been amended. Claims 14-16, 26, 31, 43, and 51 have been canceled, and new claims 54-57 have been added. Applicants thank the Examiner for the helpful telephone discussions regarding the claims on December 10, 2008, January 28, 2009, and January 30, 2009.

II. Claim Amendments

Claim 1 has been amended for clarity. Specifically, claim 1 now recites "a method of treating a *Pseudomonas aeruginosa* infection in a bacterial biofilm in the lungs of a patient in need thereof . . . ." Support for this amendment can be found, for example, at paragraph 51 and figure 1 of the specification, which describes the biofilm formed by *P. aeruginosa* in the lungs.

Claims 1, 35, 46 and 48 have been amended to replace the phrase "neutral phospholipid" with "phosphatidylcholine." Support for this amendment can be found throughout the specification, and particularly at paragraph 29 and in the examples. Claim 1 also has been amended to recite that "the lipid component and amikacin have a ratio of less than 2.5:1 by weight. Support for this amendment can be found at paragraph 49 and the table on page 20 of the specification.

Claim 32 has been amended to depend from claim 1, and also to add DSPC as a possible phosphatidylcholine. Support for this amendment can be found at paragraph 29 of the specification.

Claims 35, 46 and 48 have been amended to replace the term "neutral phospholipid" with "phosphatidylcholine," in accordance with the same amendment in claim 1.

Claim 36 has been amended to depend from claim 35.

Claim 41 has been amended for clarity by deleting the word "is."

Claim 44 has been amended to depend from claim 1. Claims 44 and 52 have been amended to recite that the lipid to amikacin ratio is "less than 1.1:1 by weight," instead of "1.0:1 or less." Support for this amendment can be found at paragraph 49 and in the table of examples on page 20 of the specification.

Claim 45 has been amended to recite that the amikacin is provided as amikacin sulfate. Support for this amendment can be found in the examples at pages 20 and 21.

New claim 54 and 55 recite that the DPPC and cholesterol have a mole ratio ranging from 19:1 to 1:1. Support for this claim can be found in the table on page 20 of the specification, which describes numerous examples of liposomal amikacin formulations having ratios of cholesterol to DPPC within the claimed range.

New claim 56 recites an embodiment of the present method, wherein the liposomal amikacin formulation comprises amikacin and a lipid component, the lipid component consists essentially of cholesterol and DPPC, the lipid component and amikacin have a ratio of less than 1.1:1 by weight and the amikacin is provided as amikacin sulfate. Support for this claim can be found throughout the application and in particular in the examples described in the table on page 20.

New claim 57 recites that the patient is a cystic fibrosis patient. Support for this new claim can be found in the claims as field and at paragraph 51 of the specification.

No new matter has been added.

III. Declaration of Meers

In the Final Office Action, the Examiner states that the Declaration of Meers, submitted with the response filed on July 28, 2008, is not persuasive because the data is not commensurate with the scope of the claims. Applicants respectfully submit that the data is commensurate with the scope of the presently amended claims. For convenience, a copy of the Declaration of Meers and exhibits are attached to this paper.

Specifically, claim 1 now recites now recites "a method of treating a *Pseudomonas aeruginosa* infection in a bacterial biofilm in the lungs of a patient in need thereof . . . ." As explained in Exhibit A of the Declaration of Meers, *P. aeruginosa* forms a biofilm in the lungs. *Exhibit A* at p. 859, column 2 – 860, column 1; p. 866, column 2; see also Specification at paragraph 51. This biofilm mode of growth presents a significant challenge to antibiotic therapy in treating *P. aeruginosa* infections in the lung. For example, the positively charged aminoglycosides do not penetrate the biofilm effectively because of electrostatic interactions.

The present claims overcome these limitations by administering to the lungs a liposomal amikacin formulation, wherein the lipid component consists essentially of a phosphatidylcholine and a sterol. As explained in the Declaration of Meers, a phosphatidylcholine and sterol

formulation has been shown to effectively penetrate both *Pseudomonas* bacterial biofilms and the sputum of cystic fibrosis patients. It is believed that this enhanced penetration allows the amikacin to reach the bacteria. *Declaration of Meers.* at ¶ 8, *Exhibit A,* p. 860, col. 1-2. Liposomes containing cationic or anionic lipids, in contrast, do not penetrate the biofilm as effectively. For example, liposomes containing a cationic lipid adhere to the negatively charged biofilm surface due to electrostatic interactions. *Id.* at ¶ 7, *Exhibit A*, at p. 866. Liposomes containing negatively charged lipids also fail to penetrate the biofilm as effectively as the neutral liposomes. It is believed that this is due to repulsion between to the negatively charged biofilm surface and the negatively charged liposome surface. *Id.* at ¶8-10.

Similarly, it is believed that aminoglycosides do not penetrate mucus, particularly mucus found in the lungs of CF patients, because of electrostatic interactions between the positive charge of the aminoglycoside and the negative charge of the mucus. As explained in Exhibit A of the Meers declaration, the liposomal formulation of the present claims is able to effectively penetrate CF mucus. *Exhibit A* at p. 860-861.

IV. Rejections Under 35 U.S.C. § 103(a)

A. Coe in combination with either Gonda or Lagace

The Examiner has rejected claims 1, 14-16, 26, and 29-53 as being unpatentable over U.S. Patent Application no. 5,540,936 ("Coe") in combination with either U.S. Publication No. 2005/0019926 to Gonda et al. ("Gonda") or U.S. Patent No. 5,662,929 to Lagace ("Lagace"). In order to establish a *prima facie* case of obviousness, the Examiner must determine the scope and content of the prior art, ascertain the differences between the claimed invention and the prior art and resolve the level of ordinary skill in the pertinent art. *Graham v. John Deere Co.*, 383 U.S. 1, 148 (1966). Once the Graham factual inquiries have been resolved, the Examiner must explain why the differences between the cited references and the claims would have been obvious to one of ordinary skill in the art. Fed. Reg. Vol. 72, No. 195, p. 57527. The Supreme Court in *KSR* stressed that "obviousness cannot be sustained by mere conclusory statements; instead there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." *KSR* 127 S.Ct. 1727, 1740 (2007); see also Fed. Reg. Vol. 72, No. 195, p. 57529.

"The key to supporting any rejection under 35 U.S.C. 103 is the clear articulation of the reason(s) why the claimed invention would have been obvious. Fed. Reg. Vol. 72, No. 195 at p. 57528. Additionally, objective evidence of nonobviousness must be considered. Such evidence, sometimes referred to as ''secondary considerations,'' may include evidence of commercial success, long-felt but unsolved needs, failure of others, and unexpected results. *Id.*

Coe describes a process for producing liposomes. *Coe* at col. 1, ll. 6-8. A bioactive agent, such as an aminoglycoside, can be associated with the liposome. *Id.* at col. 4, ll. 13-26. Importantly, Coe fails to describe administration to the lungs to treat *P. aeruginosa* nor the presently recited lipid to drug ratio of less than 2.5:1. In fact, Coe's lipid to drug ratios are much higher, ranging from 5:1 to 15:1, with 10:1 being preferred. *Id.* at col. 6, ll. 13-26.

Gonda describes compositions comprising nucleic acids complexed with a cationic aminoglycoside, where the nucleic acid is "condensed." *Gonda* at ¶ 9. The compositions of Gonda provide a "a means for introducing a nucleic acid and/or a gene product into a cell . . . ." *Id.* at ¶ 10. Nucleic acids condensed with polyvalent cationic species are less susceptible to degradation by nucleases. *Id.* at ¶ 28. In some embodiments, the cationic aminoglycoside-nucleic acid complex may be administered by inhalation. In certain embodiments of Gonda, the composition also may include one or more lipids or polymers. *Id.* at ¶ 57. Gonda provides no teaching concerning the ratio of lipid to drug.

The Lagace liposomes all comprise a negatively charged phospholipid, and explicitly prohibit the use of sterols. Specifically, Lagace explains "there is provided a low rigidity multilamellar liposomal formulation, free of cholesterol, comprising a neutral lipid an anionic lipid, and at least one therapeutic agent, wherein the liposomal formulation enhances the penetration of the therapeutic agent inside a bacterial cell." *Lagace* at col. 5, ll. 47-53 (emphasis added). Lagace further states that its liposomal formulation provides improved bactericidal activity in part because of the "original combination of phospholipids that markedly improve the penetration of a therapeutic agent in bacterial cells." *Id.* at col. 9, ll. 64-3. Thus, Lagace suggests that the inclusion of anionic lipids in the liposome is important for enhanced binding and penetration into bacterial cells.

As explained in the Declaration under 37 C.F.R. § 1.132 by Meers, Applicants have achieved unexpected results in administering a liposomal amikacin formulation, comprising amikacin and a lipid component, wherein the lipid component consists essentially of a phosphatidylcholine and a sterol, as presently claimed. As explained in the specification at p. 1, ¶4 and Exhibit A of the Declaration of Meers, the mucus of cystic fibrosis patients and bacterial biofilms, such as those associated with a *P. aeruginosa* lung infection, make the treatment of such infections difficult. As noted in paragraph 6 of the declaration, liposomes of phosphatidylcholine and sterol are able to significantly penetrate *Pseudomonas* biofilms. Experiments were conducted comparing the ability of neutral, positively charged, and negatively charged liposomes to penetrate a *Pseudomonas* biofilm. The results showed that the neutral liposome (DPPC/Chol) had significantly deeper penetration into the biofilm, and with higher concentration, compared to DPPC/DPPG/chol or DPPC/DPTP/Chol, in large biofilm patches with distinct boundaries. *Declaration of Meers* ¶ 10, Exhibits B and C. The clinical benefits seen in a Phase II clinical trial are attributed in part to this penetration capability. *Id* at ¶¶ 12-13, Exhibits D and E.

None of the cited references, taken alone or in any combination, teach or suggest that amikacin encapsulated in a phosphatidylcholine and sterol based liposome is capable of penetrating a biofilm or mucus in the lungs of a patient.

V. Conclusion

In light of the amendments and remarks set forth above, Applicants submit that the pending claims are in condition for allowance. Reconsideration and timely allowance of the pending claims is respectfully solicited. If a telephone conference would be helpful, the Examiner is invited to call the undersigned at 617-832-1223. Applicants hereby request that any additional fees required for timely consideration of this application be charged to **Deposit Account No. 06-1448, Reference TRA-008.01**

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Respectfully submitted,

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